Preface

These are exciting times in neuro-oncology. By the time this book is published I will have worked in this field for 20 years, giving me enough perspective to contemplate significant changes during these two decades. In 1989 little was known about brain tumors and the community of researchers was small. Pioneers such as Charles Wilson had the foresight to foster inter-disciplinary approaches to the brain tumor treatment and investigation. Treatment options were limited to surgery, radiotherapy, and a few modestly effective chemotherapeutic agents such as BCNU. Over the ensuing decades, the neuro-oncology field has expanded and traversed a number of “waves”, each of which was expected to yield a rapid cure. The 1980s ushered in research that tapped into the power of the immune system and promised immunotherapies, whether antibody-based or cell-based. When I entered the field there was a strong interest in identifying autocrine growth factors that drive tumor growth and the early groundbreaking genetic studies were being performed. Amplification of the $EGFR$ gene on chromosome 7 in glioblastoma had been identified as an important oncogenic event in 1984. In subsequent years, the application of karyotypic analyses and loss of heterozygosity studies pinpointed the location of tumor suppressor loci on chromosomes 9, 10, and 17. In 1989, the $p53$ gene was identified as the tumor suppressor lost from chromosome 17 in glioblastoma and other cancers. In 1993 the $p16$ cell cycle inhibitor was described and in 1997 the $PTEN$ phosphatase was discovered as a critical gene product lost due to genetic alterations on chromosome 10. Genetic discoveries in glioma spearheaded the use of similar technology for the discovery of new signaling pathways in medulloblastoma, meningioma, ependymoma, and other brain tumors.

The 1990s witnessed the advent of cancer gene therapy and anti-angiogenic therapies. The remarkable results obtained in mouse glioma models with retroviral thymidine kinase/ganciclovir gene therapy systems were not reproduced in clinical trials, yet led to new generations of virotherapy through the use of oncolytic viruses. The definition of angiogenic mechanisms and the discovery of endogenous negative regulators of these processes have led directly to clinical applications in which tumoral blood vessels are targeted by anti-angiogenic therapies, a strategy which is bearing fruit with anti-VEGF antibodies.
Subsequent breakthroughs have included the sequencing of the human genome in 2003 and the use of new techniques that permit whole-genome analyses for gene expression and alterations. The impact of these discoveries is in full bloom for glioblastoma multiforme with The Cancer Genome Atlas (TCGA), an unprecedented, NIH-sponsored, effort to identify every possible genetic and epigenetic alteration and gene expression change in 500 glioblastoma specimens. The initial results of the TCGA Research Network as well as an independent effort to sequence all genes in 22 glioblastoma have just been published. These important studies have shown that, not surprisingly, this disease is complex, with up to 60 mutated genes per tumor. Fortunately, these genes can be distilled to a lesser number of pathways that make their study more palatable. Studying 60 genes, and even fewer pathways, is certainly easier than 30,000! We know that with enough effort and research teams focusing on all these new therapeutic targets, we will be able to fully comprehend the biological complexity of the disease and further accelerate the discovery of life-saving medicines. Novel targeted therapeutics and biomarker-based imaging will benefit in the near future from the emergence of nanotechnology.

Independently, the last decade has brought major discoveries on cell lineages in the central nervous system and the differentiation events that take place from stem cells to neurons, astrocytes, and oligodendrocytes. The application of markers identified in normal CNS development to the understanding of tumor heterogeneity gave birth to the “cancer stem cell hypothesis”, a concept that has promoted a rethinking of the basic tenets in oncology and has blended the study of cancer and neuroscience. The speed of discovery summarized above is remarkable and gives no hint of slowing down. Many of these exciting developments are described within this book.

Today the prognosis of malignant brain tumors, such as glioblastoma, is still dismal, but what has changed is that there is real hope for a cure. The research efforts touched upon above and described in much more eloquent fashion by the authors in this book are bearing fruit. New biomarkers and therapeutic targets are being identified. We are seeing successful therapies emerge from the use of antibodies and cytotoxins, signaling pathway-targeted small molecules, anti-angiogenesis strategies, better use of “old-fashioned” alkylating drugs following increased knowledge of DNA repair pathways, and vaccination approaches targeting unique tumor epitopes uncovered by genetic approaches. Further development of novel therapies is advancing at rapid pace and there is an increased need for animal models to evaluate them. A full third of the book is devoted to present a comprehensive selection of the models currently available.

The light at the end of the tunnel is becoming visible. It is encouraging to witness, and exciting to participate in, the dramatic improvements in brain tumor treatment that are being made.

Atlanta, GA
March, 2009

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CNS Cancer Models, Markers, Prognostic Factors, Targets, and Therapeutic Approaches
Van Meir, E.G. (Ed.)
2009, XII, 1284 p. 160 illus., 64 illus. in color. With 2 16-page color inserts., Hardcover
ISBN: 978-1-60327-552-1
A product of Humana Press